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CONQUERING THORACIC CANCERS WORLDWIDE

Neratinib in pretreated *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC): initial findings from the SUMMIT basket trial

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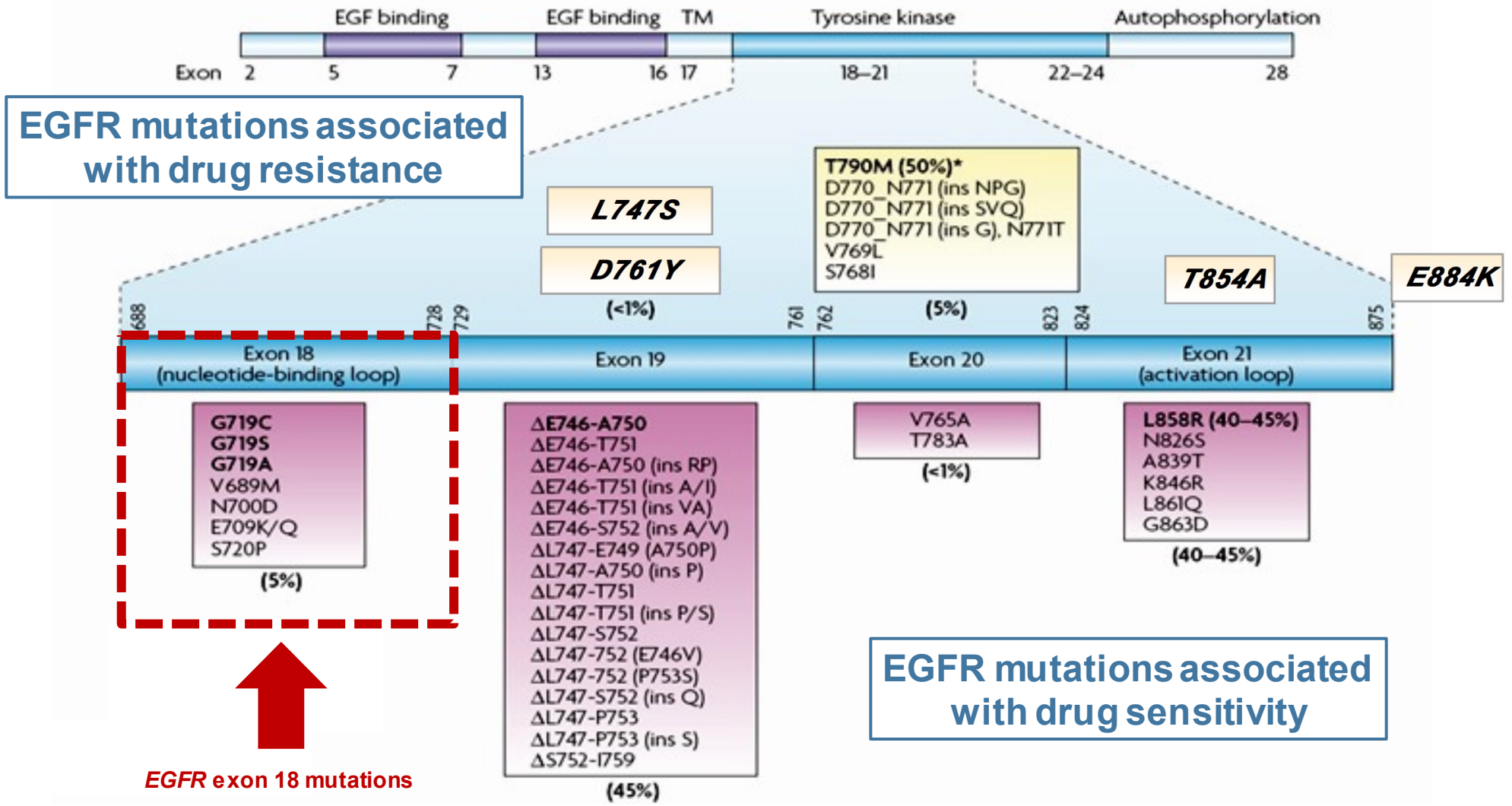
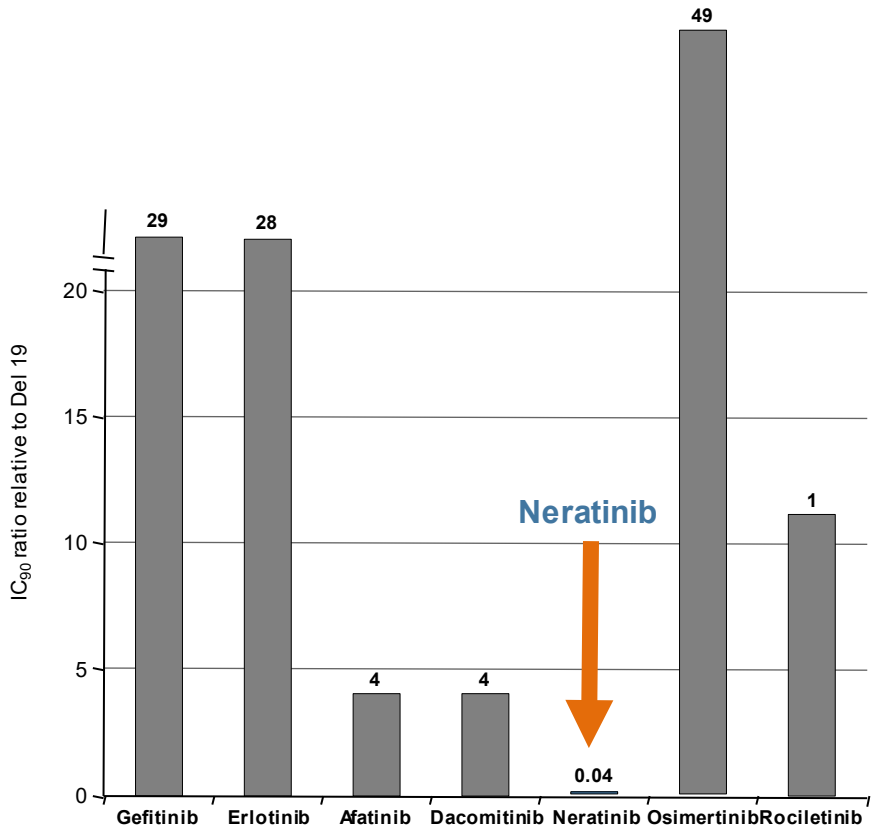
EGFR exon 18 mutations represent 5% of all *EGFR* mutations detected in lung cancer



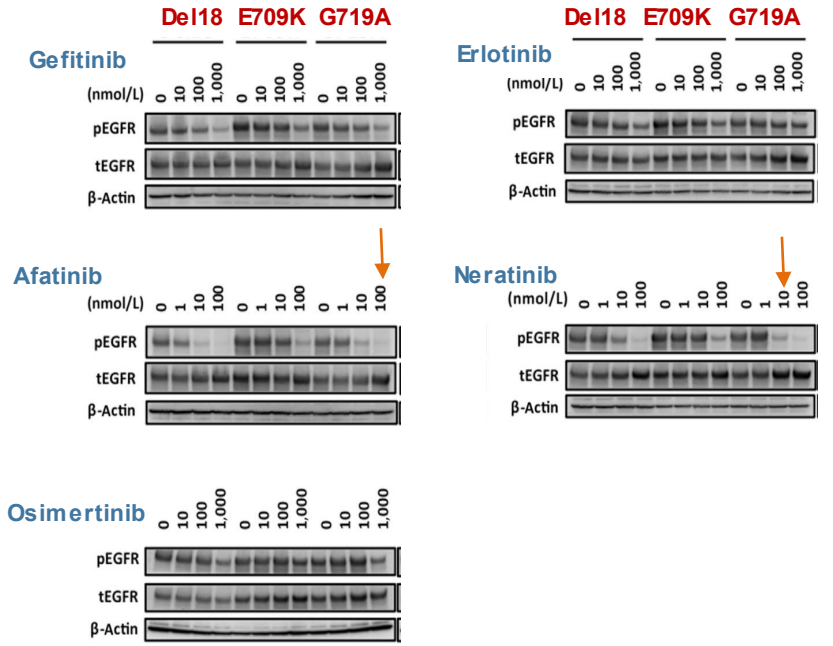
EGFR exon 18 mutations are highly sensitive to neratinib *in vitro*

Neratinib: oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), & HER4 (ERBB4)*

Comparative TKI effects in *EGFR* exon 18 (G719A) mutation-positive Ba/F3 cells#



Western blot analyses of transfected HEK293 cells



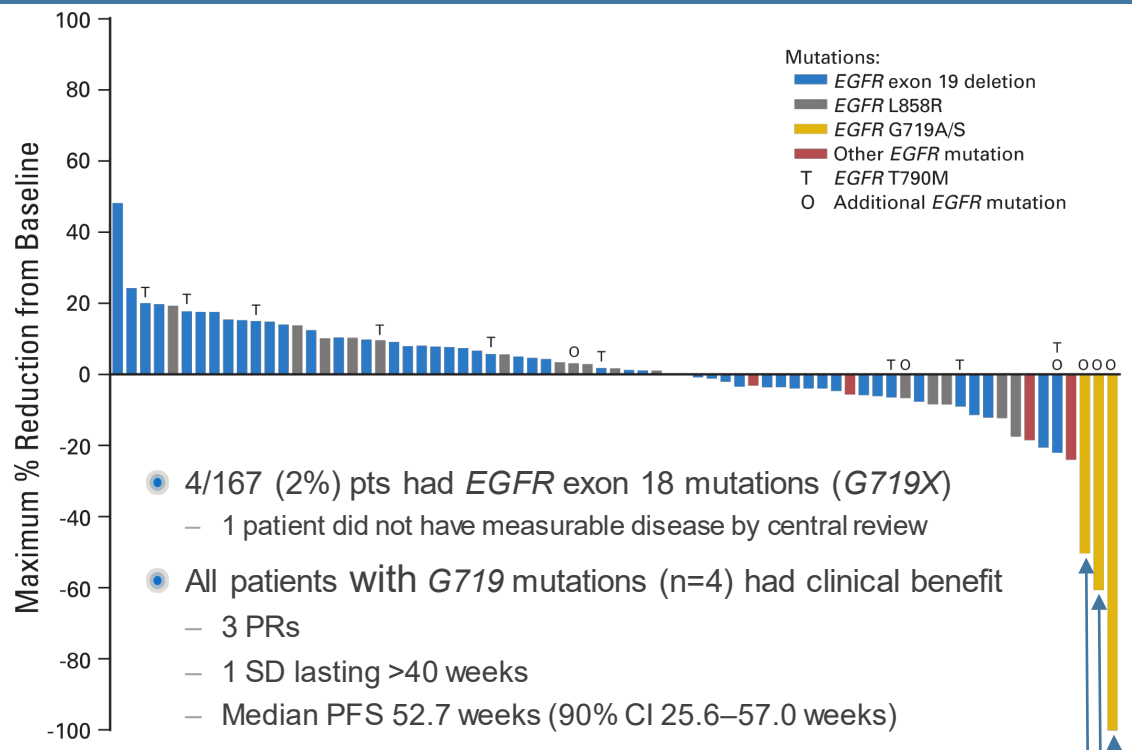
- The phosphorylation of EGFR was almost inhibited by **100 nmol/L afatinib** in Del18, E709K, G719A, and Del19 cells.
- **10 nmol/L neratinib** more effectively inhibited the phosphorylation of EGFR in G719A cells.

* Rabindran et al. Cancer Res 2004:64:3958–65; 2. Bose et al. Cancer Discov 2013;3:224–37

Modified from Kobayashi et al. Clin Cancer Res 2015;21:5305–13;

EGFR exon 18 mutations are highly sensitive to neratinib: a POC trial

Prior phase 2 trial of neratinib in EGFR TKI-refractory NSCLC



SUMMIT study design for *EGFR* exon 18-mutant lung cancer cohort

***EGFR* exon 18-mutant Lung Cancer**

Open-label, single-arm cohort

Neratinib monotherapy (240 mg, oral daily)

Mandatory Loperamide prophylaxis: oral 4 mg TID days 1–14, 4 mg BID days 15–46; as needed PRN

Key inclusion criteria

- Histologically confirmed lung cancers for which no curative therapy exists
- Documented *EGFR* exon 18 mutation by local method (any CAP/CLIA-certified lab)
- **Prior treatment with EGFR or pan-HER TKI allowed (afatinib, dacomitinib, osimertinib, etc)**
- ECOG status of 0 to 2
- RECIST 1.1 disease only

Key exclusion criteria

- Patients who are receiving any other anticancer agents
- Symptomatic or unstable brain metastases
- Women who are pregnant or breast-feeding
- Known KRAS activating co-mutation

Study endpoints and trial design features

Primary endpoint

- Objective response rate at first post-baseline tumor assessment (Week 8) (ORR_{Wk8})

Secondary endpoints

- ORR (confirmed by RECIST criteria)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

Simon 2-stage design

- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments

- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods

- ORR_{first}, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI
- DOR

EGFR exon 18-mutant lung cancer cohort: baseline characteristics

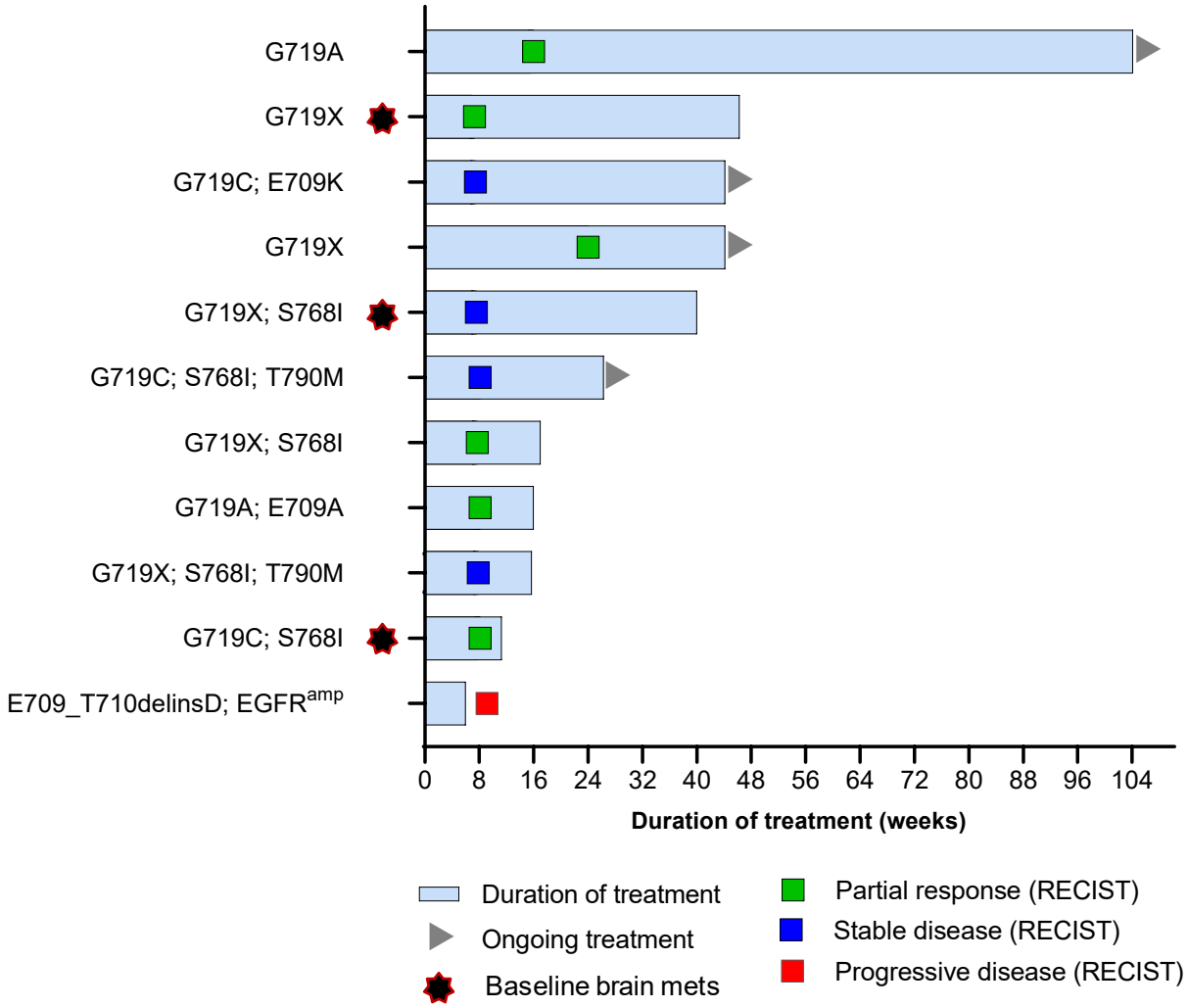
Patient characteristics	Safety/efficacy evaluable patients (n=11)
Median age, years (range)	67 (56–83)
<65 years, n (%)	4 (36)
≥65 years, n (%)	7 (64)
Gender, n (%)	
Female	5 (45)
Male	6 (55)
ECOG performance status, n (%)	
0	5 (45)
1	6 (55)
Race, n (%)	
Black or African American	1 (9)
White	10 (91)
Median number of prior therapies in metastatic/locally advanced setting (range)	2 (1–3)
Prior checkpoint inhibitor, n (%)	3 (27)
Prior chemotherapy, n (%)	6 (55)
Prior EGFR tyrosine kinase inhibitor, n (%)	**10 (91)**
Gefitinib/erlotinib	7 (58)
Osimertinib	3 (25)
Afatinib	2 (17)

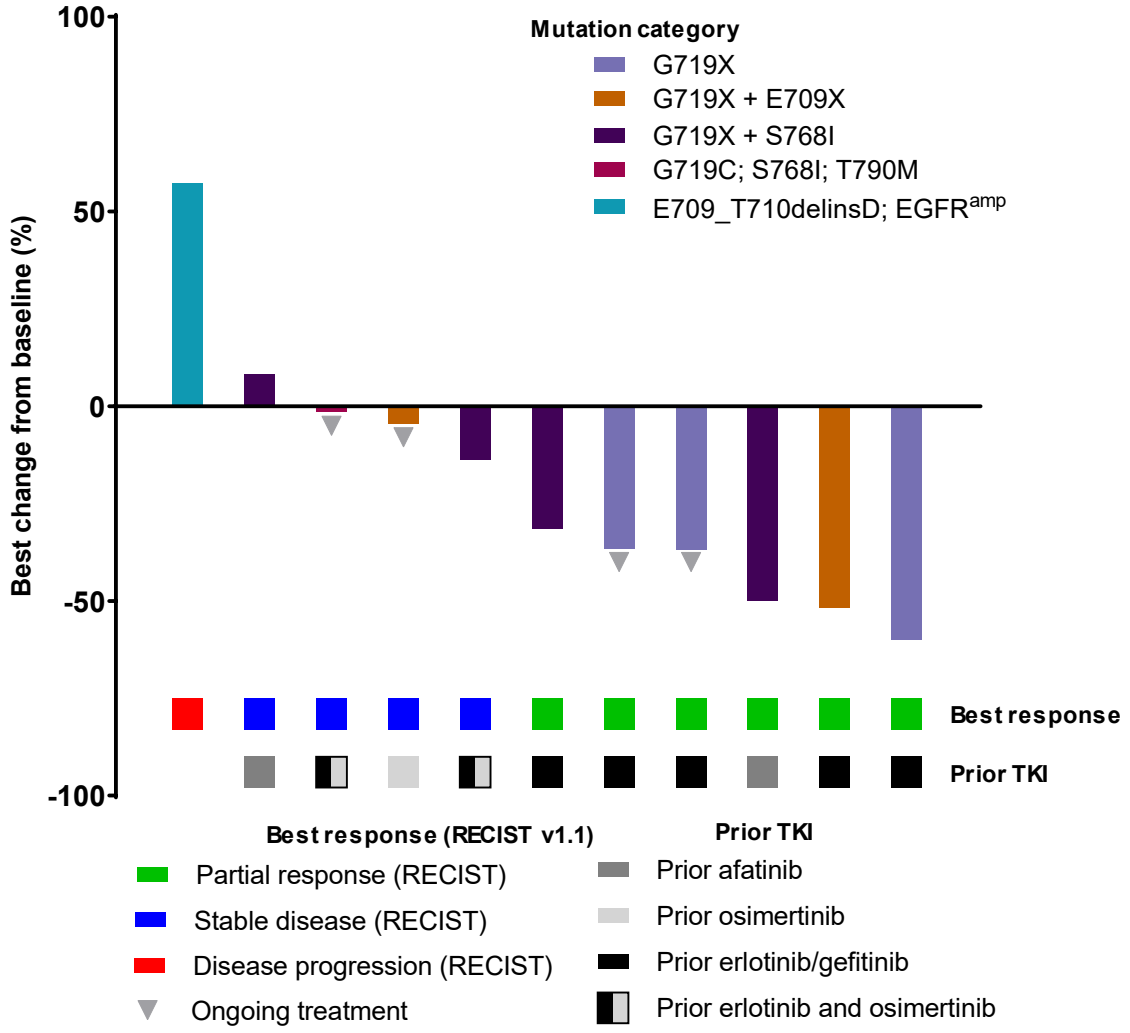
EGFR exon 18-mutant lung cancer cohort: Efficacy summary

Parameter	Efficacy evaluable patients (n=11)	TKI pre-treated subgroup (n=10)
Objective response (confirmed),[a] n	**4**	**4**
CR	0	0
PR	4	4
ORR,[a†] % (95% CI)	**36** (11–69)	**40** (12–74)
Best overall response, n	**6**	**6**
CR	0	0
PR	6	6
Best overall response rate, % (95% CI)	**54** (23–83)	**60** (26–88)
Median DOR,[b] months (95% CI)	**7.5 (4.0–NE)** **(1.9*, 4.0, 7.5, 9.2*)**	**7.5 (4.0–NE)** **(1.9*, 4.0, 7.5, 9.2*)**
Clinical benefit,[c] n	**8**	**8**
CR or PR	4	4
SD ≥16 weeks	4	4
Clinical benefit rate, % (95% CI)	**73** (39–94)	**80** (44–97)
Median PFS[b] time to event, months (95% CI)	**6.9** (2.1–NA)	**9.1 (3.7–NA)**

[a]ORR (objective response rate) defined as either a CR or PR that is confirmed no less than 4 weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis in safety population; [c]CBR (clinical benefit rate) defined as confirmed CR or PR or SD for ≥16 weeks (within +/– 7-day visit window); †Data for ORR at week 8 (ORR_{first}) and ORR (RECIST 1.1 confirmed) are identical and are only presented once. DOR, duration of response; PFS, progression-free survival, *response ongoing

EGFR exon 18-mutant lung cancer cohort: Treatment duration, best response and best change in tumor size





EGFR exon 18-mutant lung cancer cohort: Most common treatment-emergent adverse events >10%

TEAE, n (%)	Safety evaluable patients (n=11)	
	Any grade	Grade ≥3
Diarrhea	5 (45.5)	0
Vomiting	4 (36.4)	0
Constipation	3 (27.3)	0
Nausea	3 (27.3)	0
Decreased appetite	3 (27.3)	1 (9.1)
Dizziness	2 (18.2)	0
Hypertension	2 (18.2)	0
Dry mouth	2 (18.2)	0
Fatigue	2 (18.2)	0

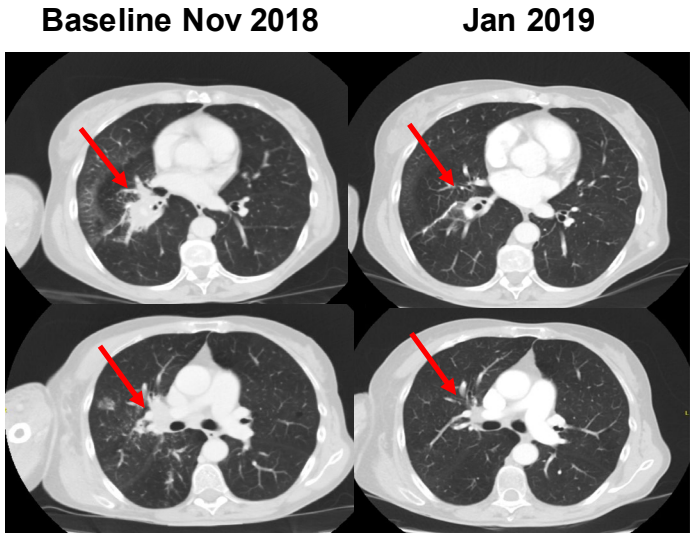
Key safety findings

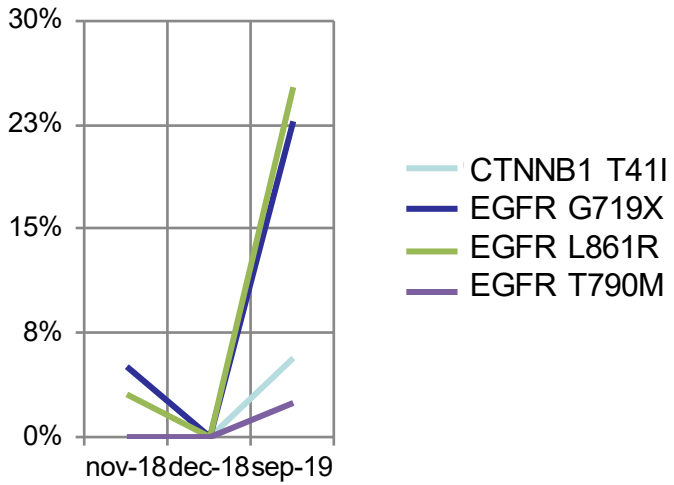
- Well tolerated with mandatory loperamide prophylaxis (first 2 cycles)
- 4 patients (36%) reported grade 1 and 1 patient (9%) reported grade 2 diarrhea
- **No evidence of grade 3 diarrhea, ILD, or skin rashes**
- No patients required a dose hold, dose reduction, hospitalization or permanently discontinued neratinib due to diarrhea

Data cut-off: 21-Aug-2020

Case study

- Female, 61 years, former smoker
- Dec 2016: stage IV lung adenocarcinoma with lung, lymph nodes, bone and brain metastasis and *EGFR* (G719X) mutation
- Dec 2016: SBRT on brain; 1st-line erlotinib achieving SD as best response and clinical benefit
- Nov 2018: asymptomatic brain/lung progression; 2nd-line neratinib (duration of treatment 46.3 weeks)
- **Jan 2019: PR (60% reduction in tumor burden by RECIST 1.1) and stable brain mets on neratinib**
- Sep 2019: lung PD; 3rd-line osimertinib





Summary/conclusions

- Single-arm phase 2 trial showing early clinical efficacy of single-agent neratinib in TKI-refractory *EGFR* exon 18-mutant NSCLC
  - Confirmed ORR: 40% & Stable disease (≥ 16 weeks): 40%
  - CBR: 80%
  - DOR: 7.5 months
  - Median PFS: 9.1 months
- Well-tolerated with no evidence of grade 3 diarrhea with mandatory loperamide prophylaxis
- No reported cases of ILD and skin rashes
- Enrollment is ongoing

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